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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/086,087	02/28/2002	Zhihao Yang	83426HEC	2857

7590 05/16/2007

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ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
05/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/086,087	YANG ET AL.	
	Examiner	Art Unit	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/8/2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1 and 3-8 are pending and examined on the merits.

This Office Action is in reply to Applicants' correspondence of 03/08/2007. Claim(s) 2 and 9 is/are cancelled; no claims are withdrawn; no claims have been newly added; claim(s) 1, 3 and 4has/have been amended.

Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put the application in condition for allowance. Any new grounds of rejection presented in this Office Action are necessitated by Applicants' amendments. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.

This Action is made **FINAL**.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Remarks Concerning the Sufficiency of the Declaration

1. Applicants have argued (pages 16-19 of the Remarks of 3/18/2007) that the Declaration submitted under 37 CFR 1.131 is sufficient to establish the conception of the claimed invention on June 5, 2001 by providing a notebook page dated on that date. Applicants' arguments have been considered but are not found to be persuasive.

With regard to the phrase 'as shown in Berkeley', Applicants have argued (page 18) that the provided declaration, which includes the statement of knowledge of section 1001 of Title 18, specifically indicates that the phrase 'refers to a published article "Effect of Flow on Complex Biological Macromolecules in Microfluidic Devices," by Polly S. Shrewsbury, Susan J. Muller, and Dorian Liepmann and published in 2001 in Biomedical Microdevices, 3:3, 225-238 by Kluwer Academic Publishers'. As such, Applicants argue that the notebook page provides adequate teaching of all of the

limitations of the claimed subject matter. This argument is not persuasive. As noted in the previous Office Action, the article allegedly referenced in the notebook page, where the provided Declaration specifies 'a published article' appeared in the September 2001 publication of the journal Biomedical Microdevices. And while the Examiner appreciates Applicants' argument (p.18 lines 28-31) that articles are not contemporaneously published upon submission, Applicant has not provided any factual evidence that the Article was indeed published prior to the date on the notebook page as to provide evidnce that the notebook page is in fact referencing the published article as stated in part 8 of the Declaration.

Furthermore it is noted that the pending claims require (part b) of claim 1) the step of 'hybridizing at least two distinct DNA sequence recognition units to said target DNA molecule' where neither the notebook page nor the allegedly referenced article provide any basis for such a limitation. The notebook page recites 'hybridize the labeled oligo-nucleotides with unknown DNA **molecules**' (with emphasis added to indicate a plurality of DNA molecules). As such there is not specific basis in the notebook page for the specific requirement that any single target DNA molecule is hybridized to 'at least two distinct DNA sequence recognition units'. Similarly, the allegedly referenced article does not provide any basis for a 'DNA sequence recognition unit' or the requirement that any single target DNA molecule is hybridized to 'at least two distinct DNA sequence recognition units'.

Applicants have not provided any argument as to how either the notebook page or 'Berkeley' provide for the limitations of the claims such as microparticles having

different shapes (claim 3), nanocrystals (claim 4), peptide nucleic acids (claim 5), or protein scaffolds or synthetic molecular moiety (claim 6); and while the article teaches a channel with the particular dimensions of 300 um wide x 60 um deep, the reference does not teach a range of widths or depths (as recited in claims 7 and 8) (see page 17 lines 21-28 of the Remarks of 3/18/2007).

For the reasons detailed above, the Declaration is insufficient to establish that Applicants conceived the claimed invention as of June 5, 2001.

As noted in the previous Office Action, the Declaration further provides (as Attachment 3) data from 'Invention Tracker' to indicate that diligence was exercised in pursuing a patent application from the time of conception to the time of filing (parts 9-11 of the Declaration). It is noted that the Attachment 3 provided with the instant Declaration provides no details regarding the recited limitations of the instant claims not provided in the 'notebook page 154'. Additionally, MPEP 715.07(a) states:

> In determining the sufficiency of a 37 CFR 1.131 affidavit or declaration, diligence need not be considered unless conception of the invention prior to the effective date is clearly established, since diligence comes into question only after prior conception is established. Ex parte Kantor, 177 USPQ 455 (Bd. App. 1958).

Thus, because conception of the invention in a scope commensurate with the requirements of the claims has not been established, the issue of any alleged exercised diligence is moot.

Maintained Rejections

Claim Rejections - 35 USC § 102

2. Claims 1 and 3-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Bensimon et al (herein referred to as Bensimon), U.S. Patent 6,054,327, 102(b) date 04/25/2000.

Several aspects of instant claim 1 part c) have been broadly interpreted by the Examiner. Passing the hybridized DNA complex "from a reservoir in a microfluidic device" is interpreted as moving any portion of the hybridized DNA complex initially in a holding area in a device designed to contain small amounts of liquids. Passing the hybridized DNA complex through a "narrow channel to cause an acceleration of flow through said channel" is interpreted as moving any portion of the hybridized DNA complex through a small passageway, which involves an acceleration of flow through the passageway.

Bensimon teaches a method of analyzing DNA comprising hybridizing the DNA in solution with probes having fluorescent reagents and then detecting the position of the probes after aligning ("causing said hybridized DNA complex to extend into a substantially linear configuration", instant claim 1 part c)) the DNA (instant claims 1, 5 and 6; see column 16, lines 50-55, and Fig. 6 of Bensimon). Bensimon also teaches that DNA molecules placed in a channel between cover slips can be aligned by the evaporation flow parallel to a moving meniscus in the channel (instant claim 1 part c); see column 2, lines 11-12 and column 3, line 22 and Fig. 6 of Bensimon). Regarding this method of aligning DNA described by Bensimon, DNA molecules in a random coil state fixed at a location in a channel between cover slips is interpreted as the embodiment of the hybridized DNA complex initially being in a "reservoir in a microfluidic device" as recited in instant claim 1 part c). In addition, as the meniscus

initially moves through the channel between the cover slips, there will be an acceleration of fluid flow in the channel and a portion of the DNA complex will pass through the channel as it extends to a linear configuration (see Fig. 6 of Bensimon). This is interpreted as the embodiment of passing the hybridized DNA complex through a "narrow channel to cause an acceleration of flow through said channel, thereby causing said hybridized DNA complex to extend into a substantially linear configuration;" (recited in instant claim 1 part c)). Bensimon teaches that the probes used to hybridize to DNA can be oligonucleotides, RNA, DNA, and peptide nucleic acids (instant claims 5 and 6; see column 13, lines 21-23 and 64-65 of Bensimon) which identify a specific sequence of DNA by hybridization, and specifically recites the use of multiple probes (which are at least two probes) for the analysis of a DNA molecule (col 13 lns.12-24). Bensimon also teaches that oligonucleotide probes can be labeled with microbeads (instant claims 1, 3 and 4; see column 11, lines 20-41 and column 14, lines 4-7 of Bensimon). With regard to instant claim 1 part d) Bensimon teaches in situ mapping comprising the detection of multiple probes on an aligned DNA molecule (see column 16, lines 50-55 of Bensimon). Relevant to parts e) and f) of claim 1, Bensimon teaches the analysis of the entire length of a linear labeled nucleic acid molecule (e.g. Fig 8) which allows for determining the sequential order of labels on the target, and specifically teaches the use of multiple probes to determine the position or size of multiple specific sequences, which is identification of the target DNA molecule.

Response to Remarks

Applicants traverse the rejection of claims under 35 USC 102 as anticipated by Bensimon. Applicants argue (pages 4-10) that the phrase 'passing said hybridized DNA complex in a random coil state in a fluid carrier from a reservoir in a microfluidic device through a narrow channel' requires that the entirety of a DNA molecule pass into one opening, though a channel structure, ad out another opening such that the entire molecule is no longer within the channel. As such, Applicants argue that Bensimon fails to teach passage of a hybridized complex from a reservoir through a narrow channel. This argument is not persuasive for the reasons detailed in the Non-Final Office Action of 9/25/2006. The Examiner maintains that the claims do not provide any structural definition of what is required of a 'reservoir' or a 'channel', and as such the use of the terms in the claims, given their broadest reasonable interpretations, merely set forth that the hybridized DNA complex is moved from one portion of a device to another. It is further maintained that the limitation that a hybridized DNA complex is moved through a channel requires only that a portion of a molecule move within a channel and that Bensimon teaches such a movement (for example Figure 6 of Bensimon shows a DNA complex (where the non-fixed end of the molecule is the complex) that passes from a reservoir (its original position at the top of Figure 6) through a channel (where the channel is where the non-fixed end is at the bottom of Figure 6). And while the instant specification may provide a particular embodiment of the claimed method wherein an entire molecule is passed from one distinct part of a device with particular dimensions, through a second part of a device with particular dimensions, and into a third part of a device with particular dimensions, such a particular embodiment does not change the

fact that the teachings of Bensimon satisfy the limitations of the claims as written and broadly but reasonably interpreted.

The rejection as set forth is **MAINTAINED**.

3. Claims 1, and 3-6 are rejected under 35 U.S.C. 102(e) as being anticipated by Chan et al (hereinafter referred to as Chan-1) Pre Grant Publication 2003/0059822, 102(e) date 09/18/2001.

Chan-1 teaches a method of analyzing a polymer comprising labeling the polymer with first and second unit specific makers (thus at least two sequence recognition units, as required by the claims), the first unit specific marker having a first label and the second unit specific marker including a second label distinct from the first label; exposing the labeled polymer to a detection station to produce distinct detection signals from the first and second labels; and identifying the distinct first and second signals (instant claim 1; see page 1, para 0008 of Chan-1). Chan-1 also teaches that the first unit specific marker can be different than the second unit specific marker, either in its nature or in the polymer unit it recognizes and binds to (instant claim 1; see page 1, para 0009 of Chan-1). Relevant to parts e) and f) of claim 1, Chan-1 teaches determining the sequential order of the labels of the labeled target (e.g. Fig 8) and thus determining the order of the specific sequence of the target to identify the target DNA molecule. Chan-1 also teaches that the first unit specific marker can be identical to the second unit specific marker, yet the first and second unit specific markers are labeled with distinct labels (instant claim 1; see page 1, para 0009 of Chan-1). Chan-1 also

teaches that the polymer is preferably a nucleic acid that is genomic DNA (instant claim 1; see page 2, para 0013 of Chan-1) and that the unit specific marker can be a nucleic acid probe (instant claims 5 and 6; see page 8, para 0076 of Chan-1), or a peptide or polypeptide or peptide-nucleic acids (instant claims 5 and 6; see page 8, para 0077 of Chan-1). Chan-1 teaches that unit specific markers are attached to optically distinguishable labels that include a nanoparticlea, colloid gold nanocrystals, and micro beads (instant claims 1, 3 and 4; see page 3, para 0015 of Chan-1). Chan-1 teaches that the pattern of binding of the unit specific markers to the polymer may be determined using a variety of systems including a linear polymer analysis system (instant claim 1; see page 3, para 0033 of Chan-1) such as optical mapping or DNA combing. Chan-1 teaches that the unit specific marker (and thus the polymer) can be sequentially exposed to a station, "station" defined as a region where a portion of the polymer is exposed to an energy source in order to produce a signal or polymer dependent impulse, by movement of the marker and the station relative to one another (instant claim 1; see page 12, para 0109 of Chan-1). Chan-1 teaches that the polymer can be aligned and stretched before it reaches the interaction station and that a very effective technique of stretching DNA is to pass the polymer through a tapered microchannel having an obstacle field, followed by a constant-shear section to maintain the stretching obtained and straighten out any remaining coiling in the polymer (embodiment of "passing said hybridized DNA complex" in instant claim 1 part c); see page 13, para 0125 and page 14, para 0128 of Chan-1). Chan-1 also teaches that pressure flow is the preferred driving force of the DNA through such a microchannel recited above (see

page 14, para 0128 of Chan-1). With regard to instant claim 1 part d), Chan-1 teaches detecting optically distinguishable DNA sequence recognition units in a sequential manner along a substantially linear hybridized DNA complex (see page 1, para 0008 and page 3, para 0033 of Chan-1, also Figure 2).

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 102(e) as anticipated by the teachings of Chan-1. Applicants argue (page 12 of Remarks) that Chan-1 fails to teach passing a hybridized DNA complex in a random coil state in a fluid carrier from a reservoir in a microfluidic device through a narrow channel to cause an acceleration of fluid flow. This argument has been considered but is not found to be persuasive. The teachings of Chan-1 specifically include that molecules may be moved by fluid flow (page 12 para 109), and that the molecules may travel from an entrance region through a triangular microchannel comprising microposts (page 13 para 125) and includes that the microchannel comprising microposts is a tapered microchannel. The teaching of Chan-1 of the movement of fluid through a tapered microchannel necessarily result in an acceleration of fluid. Furthermore the teaching of Chan-1 that molecules are released from interaction with a micropost (page 14 para 127) requires an acceleration component as the speed of the molecules and fluid in the system changes during the interaction with, and subsequent release from, the microposts in the microchannel.

Applicants have further argued (page 13 of Remarks) that the Declaration submitted under 37 CFR 1.131 establishes the date of the claimed invention as prior to the applicable 102(e) date of Chan-1. The insufficiency of the Declaration in establishing the date of invention has been addressed earlier in this Office Action. Applicants have further argued that the Declaration shows that Applicants diligently pursued constructive reduction to practice in the form of the currently pending patent application. The issue of diligence has been addressed earlier in this Office Action.

The rejection as set forth **is MAINTAINED.**

4. Claims 1, and 3-8 are rejected under 35 U.S.C. 102(e) as being anticipated by Hannah et al (hereinafter referred to as Hannah; U.S. Patent 6,767,731 B2, 102(e) date 08/27/2001).

Hannah teaches a method of sequencing a target nucleic acid comprising hybridization of the target DNA with probes, which can be oligonucleotides and oligonucleotide analogs that are uniquely and detectably labeled, using a microfluidic device to pass the hybridized nucleic acid through a microchannel to extend it to an approximate linear conformation by hydrodynamic focusing, and detecting the spectral signature of each labeled probe (thus teaching multiple probes, which includes at least two probes), preferably in sequential order (instant claims 1, 5 and 6; see column 2, lines 38-44 and 51-56, and column 3, lines 3-7 and 9-11 of Hannah). Relevant to parts e) and f) of claim 1, Hannah teaches that the labels of multiple probes may be detected in a linear fashion (thus sequential detection) to determine the probe order and identify

the target DNA molecule (col.17 – Example 3). Hannah also teaches that nucleic acid molecules sequenced by this method can be DNA or RNA (instant claim 1; see column 4, lines 62-65 of Hannah). Hannah also teaches that the probes used for this method can be DNA, RNA, or analog thereof, such as a peptide nucleic acid (instant claims 5 and 6; see column 6, lines 30-34 of Hannah). Hannah also teaches that the probe labels can be fluorescent, luminescent, radioactive, phosphorescent, chemiluminescent, enzymatic, spin, electron dense, mass spectroscopic, semiconductor nanostructures, and quantum dots (instant claims 2-4; see column 8, lines 42-47 and column 10, lines 12-37 of Hannah). Hannah also teaches that photolithography can be used to obtain microchannels for use in linearizing DNA in the range of tens of micrometers wide and deep (instant claims 7-9; see column 12, lines 14-16 of Hannah). With regard to instant claim 1 part d), Hannah teaches analyzing the linear order of probes on a target nucleic acid where each probe has a distinct spectral signature (see column 2, lines 38-44 and 51-56, and column 3, lines 3-7 and 9-11 of Hannah).

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 102 as anticipated by Hannah. Applicants argue (p.15 of Remarks) that Hannah fails to teach the required limitation of an optically distinguishable material, and that the probes disclosed in Hannah are detectable only upon being exposed to an excitation source whereas the instant claims require 'colored microparticles'. This argument has been fully and carefully considered but is not found to be persuasive. Initially it is noted that

the specification of the instant application provides no limiting definition for the term 'colored microparticles', and the instant claims recite no structural limitations for the required 'colored microparticles', though the specification does indicate the breadth of the term as used in the specificion (for example on page 6 lines 8-10). Further, the teachings of Hannah include that the detectable material can be altered to provide various emission spectra, and specific includes that the emission may be in the visible portion of the light spectrum (col.9 lns.30-40). That particular embodiments of Hannah require excitation to result in emission does not take away from the anticipation of the claims as there is no negative limitation of the required method wherein the method must not include an excitation of the 'colored microparticles'.

Applicants further assert that the Declaration under 37 CFR 1.131 establishes the date of invention of the instantly claimed method as prior to the applicable 102(e) date of Hannah. The insufficiency of the Declaration has been detailed earlier in this Office Action.

The rejection as set forth is MAINTAINED.

Withdrawn rejection

5. The previously set forth rejection of claims as anticipated by the teachings of Chan et al PCT/US00/22253 (WO 01/13088) herein referred to as Chan-2 is withdrawn in light of the amendments to the claims requiring that the optically distinguishable material comprises colored microparticles. The previous rejection did not set forth that Chan-2 teaches the use of colored microparticles, as required by previous claim 2, where claim 2 has been cancelled and the limitations of claim 2 have been incorporated

into the independent claim, claim 1. Further, Chan-2 does not specifically teach the hybridization of detection of two distinct DNA sequence recognition units.

Maintained Rejections
Claim Rejections - 35 USC § 103

6. Claims 7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chan-1 Pre Grant Publication 2003/0059822, in view of Chan-2 et al (PCT/US00/22253, International Publication Number WO 01/13088 A1).

Chan-1 teaches a method of analyzing a polymer comprising labeling the polymer with first and second unit specific makers (thus at least two sequence recognition units, as required by the claims), the first unit specific marker having a first label and the second unit specific marker including a second label distinct from the first label; exposing the labeled polymer to a detection station to produce distinct detection signals from the first and second labels; and identifying the distinct first and second signals (instant claim 1; see page 1, para 0008 of Chan-1). Chan-1 also teaches that the first unit specific marker can be different than the second unit specific marker, either in its nature or in the polymer unit it recognizes and binds to (instant claim 1; see page 1, para 0009 of Chan-1). Relevant to parts e) and f) of claim 1, Chan-1 teaches determining the sequential order of the labels of the labeled target (e.g. Fig 8) and thus determining the order of the specific sequence of the target to identify the target DNA molecule. Chan-1 also teaches that the first unit specific marker can be identical to the second unit specific marker, yet the first and second unit specific markers are labeled with distinct labels (instant claim 1; see page 1, para 0009 of Chan-1). Chan-1 also

teaches that the polymer is preferably a nucleic acid that is genomic DNA (instant claim 1; see page 2, para 0013 of Chan-1) and that the unit specific marker can be a nucleic acid probe (instant claims 5 and 6; see page 8, para 0076 of Chan-1), or a peptide or polypeptide or peptide-nucleic acids (instant claims 5 and 6; see page 8, para 0077 of Chan-1). Chan-1 teaches that unit specific markers are attached to optically distinguishable labels that include a nanoparticles, colloid gold nanocrystals, and micro beads. Chan-1 teaches that the pattern of binding of the unit specific markers to the polymer may be determined using a variety of systems including a linear polymer analysis system (instant claim 1; see page 3, para 0033 of Chan-1) such as optical mapping or DNA combing. Chan-1 teaches that the unit specific marker (and thus the polymer) can be sequentially exposed to a station, "station" defined as a region where a portion of the polymer is exposed to an energy source in order to produce a signal or polymer dependent impulse, by movement of the marker and the station relative to one another (instant claim 1; see page 12, para 0109 of Chan-1). Chan-1 teaches that the polymer can be aligned and stretched before it reaches the interaction station and that a very effective technique of stretching DNA is to pass the polymer through a tapered microchannel having an obstacle field, followed by a constant-shear section to maintain the stretching obtained and straighten out any remaining coiling in the polymer (embodiment of "passing said hybridized DNA complex" in instant claim 1 part c); see page 13, para 0125 and page 14, para 0128 of Chan-1). Chan-1 also teaches that pressure flow is the preferred driving force of the DNA through such a microchannel recited above (see page 14, para 0128 of Chan-1). With regard to instant claim 1 part

d), Chan-1 teaches detecting optically distinguishable DNA sequence recognition units in a sequential manner along a substantially linear hybridized DNA complex (see page 1, para 0008 and page 3, para 0033 of Chan-1, also Figure 2).

Chan-1 teaches stretching DNA by passing the DNA through a microchannel, but is silent with respect to the width or depth of the channel (see page 13, para 0125 and page 14, para 0128 of Chan-1).

Chan-2 teaches that a channel with 1 μm depth, 1 mm length, and a shear rate of 0.25/s gives a force of approximately 0.25 pN, which the inventors have verified experimentally is adequate to stretch DNA (instant claims 7 and 8; see page 25, line 16 of Chan-2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to perform the method of Chan-1 with the device of Chan-2 because Chan-2 specifically teaches a device for performing the method of Chan-1. The ordinary artisan would have been motivated to use the device of Chan-2 because Chan-1, while generally teaching a method of stretching DNA with a microfluidic device, is silent with regard to the specific structure and dimensions of the device. The device, with its specific dimensions, taught by Chan-2 functions to stretch DNA as taught by Chan-1. The ordinary artisan would be motivated to use the device of Chan-2 in the method of Chan-1 because Chan-1 teaches to stretch DNA by passing the DNA through a microchannel, but no specific structure or dimensions of the microchannel are recited.

Response to Arguments

Applicants have traversed the rejection of claims under 35 USC 103 as obvious in view of the teachings of Chan-1 in view of Chan-2. Applicants argue (pages 24-25 of Remarks) that the Declaration under 37 CFR 1.131 establishes the date of invention of the instantly claimed method as prior to the applicable 102(e) date of Chan-1. The insufficiency of the Declaration has been detailed earlier in this Office Action.

Further with regard to the Applicants argument (page 24 of remarks) that not all exhibits of the declaration need to support all of the claimed limitations (regarding the ranges of 'from about o.1 μm to about 500 μm' in claim 7 and 'from about 1 μm to about 300 μm' in claim 8), provided that any missing limitation is supported by the declaration itself, the Examiner maintains that the Declaration does not provide support for the claimed ranges. For example, such ranges are not detailed in the notebook page, and the provided published article (Shrewsbury et al) provides only a specific microfluidic device having a width of 300 μm and a depth of 60 μm (p.226 – Device fabrication). Thus the Declaration in fact does not support the claimed ranges.

The rejection as set forth is MAINTAINED.

7. Claims 1, 3 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chan et al PCT/US00/22253 (WO 01/13088 publication date 02/22/2001, herein referred to as Chan-2) in view of Bensimon et al (U.S. Patent 6,054,327).

Chan-2 provides methods for the sequence analysis of a single nucleic acid molecule by visual examination of a nucleic acid molecule stretched into a linear conformation.

Chan-2 teaches (e.g. page 22) methods comprising extrinsically labeling a target nucleic acid sequence using an oligonucleotide (which is a DNA sequence recognition unit that identifies a specific sequence of DNA in a target, termed in the reference a 'unit specific marker') to which a label such as a fluorescent dye (which is an optically distinguishable material) is attached, relevant to part a) of claim 1. Relevant to part b) of claim 1, Chan-2 teaches that a labeled oligonucleotide can be hybridized to a target DNA to 'mark' a specific target sequence in the target (e.g. page 22), teaches that any particular target DNA may be hybridized to more than one marker (p.23 lns.3-6), and teaches the target DNA may be 'marked' when it is in a random coil state (e.g. page 45). Relevant to part c) of claim 1, Chan-2 teaches passing the labeled target DNA through a channel in a fluid carrier to cause the target:label complex to extend into a linear conformation (e.g.: p.39 ln.30; p.45 Example 6.2; Figs 9 and 15), and that the effect of accelerated fluid flow causes the target DNA to extend (e.g.: p.29 - Branched Channels; p.27 – Funnel Structures). Relevant to part d) of claim 1, Chan-2 teaches the detection of the labels on the target DNA along the length of the target (e.g. Figs 26-28; p.45 lns.1-11) thus allowing for the sequential detection of the label. Relevant to parts e) and f) of claim 1, Chan-2 teaches that the method can be used to analyze polymers to determine polymer sequence (e.g. p.22 lns.28-33), which is a determination of the sequential order of the labels of the DNA sequence recognition unit thereby identifying the target DNA molecule.

Chan-2 does not specifically teach the labeling of oligonucleotide probes with microparticles.

Bensimon teaches methods for the analysis of linearized target nucleic acid molecules using oligonucleotide probes, and teaches that oligonucleotide probes can be labeled with fluorescent labels and microbeads (instant claims 2-4; see column 11, lines 20-41 and column 14, lines 4-7 of Bensimon).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the oligonucleotide labeling techniques taught by Bensimon et al to analyze oligonucleotide probes hybridized to target DNA molecules in the methods of Chan-2. One would have been motivated to use the techniques of Bensimon et al based on the assertion of Bensimon that such methods are suitable for the detection of probes hybridized to a single target DNA molecule stretched into a linearized conformation.

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 103 as obvious over the teachings of Chan-2 in view of Bensimmon. Applicants argue (p.27 of Remarks) that Bensimmon fails to disclose passing a hybridized DNA complex from a reservoir in a microfluidic device through a narrow channel. This argument is not found to be persuasive because in the rejection Bensimon is not used to provide any teachings of passing a complex from a reservoir through a channel, where such teachings are provided by Chan-2 (see for example Fig 14 and 15 of Chan-2).

Applicants further argue that neither Bensimon nor Chan-2 disclose attaching colored microparticles to a DNA sequence recognition unit or detecting two or more

microparticles on at least two microparticles on two sequence recognition units. This argument is not found to be persuasive because Bensimon does teach aspects of sequence recognition units with microparticles (for example col.11 lns.33-38), and also teaches aspects of using multiple probes (which are sequence recognition units) on a single target molecule to specifically detect individual probes (e.g.: Bensimon col.13 lns.18-25 and col.16 ln.1-4).

The rejection as set forth is **MAINTAINED.**

Conclusion

8. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your

questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days.

Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Stephen Kapushoc
Art Unit 1634

BJ FORMAN, PH.D.
PRIMARY EXAMINER